REMARKS/ARGUMENTS

Claims 57, 59-70, 101 and 112 are pending in the present application. Support for new claim 112 finds support in the specification, for example, at page 8, lines 30-31. Applicants note that in the previous response claims 62 and 66-68 were amended to refer to claim 57, instead of claim 59. The claims, however, were mistakenly identified as "Previously presented", rather than "Currently amended." The current listing of claims is believed to be accurate.

Applicants acknowledge the election of a single species (ST3GalIII sialyltransferases). The Examiner indicated that claim 66 is withdrawn from consideration because ST3Gal III allegedly does not recognize O-linked carbohydrates. As noted in the previous response, should a generic claim be found allowable, consideration of the non-elected species is required.

In the Office Action, the Examiner rejects claims 68-70 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for use of the term "sialyl motif." Claims 57, 59-65. 67-70, and 101 are rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Bergh *et al.* (US Patent 5,272,066), Maras *et al.* (USP 5,834,251), Weinstein *et al.* (*J. Biol. Chem.*, 257:13845) and Williams *et al.* (*Glyconconjugate J.* 12:255). Claims 57, 59-65, 67-70 and 101 are rejected under the doctrine of obviousness-type double patenting over claims in the parent patent US Patent 6,399,363). Each of these rejections will be addressed in the order in which they were raised.

Rejection under 35 U.S.C. § 112, second paragraph

The rejection of claims 68-70 is overcome by the above amendments to claim 68. In the Office Action, the Examiner asserted that the claims are indefinite for failing to identify the reference sequence that defines the sialyl motif recited there. Applicants have amended claim 68 to refer explicitly to SEQ ID NO: 1, which is the sequence of the sialyl motif referred to in claim 68. Support for the amendment is found on page 3, lines 5-9 and in the sequence listing. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

The rejection of the claims over the cited prior art is respectfully traversed. The Examiner cites Bergh *et al.* and Maras *et al.* for teaching *in vitro* methods of enzymatic modification of glycoproteins using sialyltransferases, including ST3Gal III. The Examiner acknowledges, however, that neither reference teaches a commercial-scale method, nor does either reference discuss the extent of sialylation achieved in the methods. The Examiner cites Weinstein *et al.* for allegedly teaching conditions under which sialyltransferases can fully sialylate a substrate. Williams *et al.* is cited for allegedly teaching large scale recombinant expression of sialyltransferases. As explained below, the cited references fail to establish a proper *prima facie* case of obviousness of the claimed invention. Moreover, the applicants provide evidence that the methods of the invention have enjoyed commercial success, which is evidence of the non-obviousness of the invention.

It is well settled that to establish a *prima facie* case of obviousness, the Examiner must meet three basic criteria. First, the Examiner must show that there is some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, the Examiner must show a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) and MPEP § 2142. To support the rejection, the examiner must "present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985) and MPEP § 2142.

As noted above, the Examiner relies on the primary references (Bergh *et al.* and Maras *et al.*) for teaching *in vitro* modification of glycoproteins, and cites Williams *et al.* for large scale expression of recombinant glycosyltransferases. In the Office Action, while acknowledging the failure of the primary references to teach large scale methods, the Examiner states that one of skill would be motivated to scale up the prior art methods in light of the large

quantities of enzyme made available by the recombinant expression systems of the William *et al.* publication.

In the present rejection, the Examiner has not pointed to any specific teaching of large scale production of modified glycoproteins in the cited art. Indeed, Williams *et al.*, on which the Examiner relies for suggesting large scale methods, carries out all of sialylation reactions in a total volume of 60 μl (*see*, Williams *et al.*, page 756, first column). It is well established that the prior art must teach or suggest ***all*** the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970). In the absence of a showing of a specific teaching of large scale methods, the rejection is improper and should be withdrawn.

Moreover, applicants respectfully submit that the rejection as applied to new claim 112 is improper. Claim 112 is directed to methods of the invention in which recombinantly produced enzymes are used in the methods of the invention. As explained in the specification, large scale methods of glycoproteins require certain minimum levels of efficiency to be practical at the commercial scale. The Examiner, however, provides no reasoning or evidence to show that one of skill would have a reasonable expectation that recombinantly produced enzymes could be successfully used in commercial scale methods that achieve high level of sialylation as claimed here.

Indeed, the art cited by the Examiner (Williams *et al.*) actually provides evidence as to why one of skill would ***lack*** a reasonable expectation that recombinantly produced sialytransferases would retain appropriate kinetic properties to render them practical in a commercial scale synthetic method. As the title suggests, Williams *et al.* compared the kinetic properties of recombinant sialyltransferases to those of corresponding native enzymes. As shown in Tables 1 and 2 and discussed on page 759 in the paragraph bridging the left and right columns, the recombinant proteins generally had lower affinity (higher K_m) for substrate (CMP-NeuAc, oligosaccharide or glycoprotein), as compared to the native enzymes. Moreover, the authors found that the specific activity of the recombinantly produced α2,3 sialyltransferase had a specific activity about 1/3 of that of the native enzyme (*see* page 760, bottom of left column). The authors speculate in the Discussion Section on page 759, that differences in glycosylation in the recombinantly produced enzymes may account for the alterations in the kinetic properties.

Thus, to maintain the present rejection, the Examiner must provide a convincing line of reasoning as to why the artisan would use recombinant enzymes in the methods of the invention, in light of the evidence that the kinetic properties of recombinant enzymes are not the same as native enzymes. In the absence of such a showing, applicants respectfully submit the rejection is improper and should be withdrawn.

Even assuming that a *prima facie* case of obviousness is improperly maintained, Applicants provide evidence of the nonobviousness of the invention with this response. Affidavits or declarations containing evidence of criticality or unexpected results, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, and the like, must be considered by the examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. §103 (MPEP §716.01(a)).

As explained on pages 1 and 2 of the present application, the circulatory lifetime of therapeutic glycoproteins in the blood is highly dependent on the presence of terminal sialic acids on the carbohydrate portion of the protein. It has long been recognized that ensuring the presence of terminal sialic acids on carbohydrate groups of therapeutic glycoproteins is an important consideration for their commercial development. Currently used methods of recombinant production of these proteins (*e.g.*, mammalian cell culture) do not provide optimal glycosylation. Since the most important problems associated with glycosylation of commercially important recombinant glycoproteins, involve terminal sialic acid, a need has long existed for methods that enzymatically "cap" carbohydrate chains that lack a terminal sialic acid. At the time of the present invention, no commercially feasible methods of solving this problem were known.

In the issued parent (US Patent No. 6,399,930), applicants submitted a Declaration by Dr. David A. Zopf, ("the Zopf Declaration") Vice President of New Product Development of Neose Technologies, Inc showing that the present invention addressed this long felt need in the art. Dr. Zopf provides evidence of the high level of interest in the claimed methods and their resulting commercial success. In addition, the Zopf Declaration shows that an expert in the field questioned the feasibility of the present invention. Thus, the enclosed

Declaration presents secondary indicia of nonobviousness sufficient to rebut any *prima facie* case of obviousness.

As evidence of the skepticism by an Expert, Exhibit 1 of the Zopf Declaration is a letter from Dr. James E. Bailey, Institute of Biotechnology, ETH-Zürich. The letter expresses disbelief that an *in vitro* glycosylation process is commercially viable. Dr. Bailey states:

> ...the process complications and costs associated with producing and utilizing a glycosyltransferase and donor substrate make the exogenous manipulation of glycosylation far less attractive than engineering the cells to maximize the production of the desired glycoform.
>
> Failure of much simpler cofactor-requiring enzyme catalyzed reactions to gain industrial success in competition with whole-cell biocatalysts speaks very strongly in my opinion *against* the competitive prospects of *in vitro* remodeling of glycosylation." [Emphasis added].

Under M.P.E.P. § 716.05, this skepticism by an Expert, constitutes strong evidence of nonobviousness of the claimed invention.

The Zopf Declaration also shows that the present invention has enjoyed commercial success and that there is nexus between the claimed invention and its commercial success. Under M.P.E.P. § 716.03, this too is strong evidence of nonobviousness.

As set forth in paragraph 6, of the Zopf Declaration, Dr. Zopf has directly negotiated use agreements of the claimed technology with over 20 companies to assess the feasibility of the technology for *in vitro* sialylation of recombinant therapeutic glycoproteins in development. All feasibility studies referred to in his declaration have been successful. As set forth in his declaration, many of these successful feasibility studies have led to ongoing negotiations for commercial licenses to the technology for large-scale manufacture of human glycoprotein therapeutics. In addition, the present technology is being employed as an essential part of ongoing collaborative research and development agreements with other companies to develop commercial manufacturing methods for cancer vaccines and treatments for neurological diseases.

Further, as is set forth in paragraph 7, a consistent improvement in glycosylation was experienced when various companies used the claimed invention. The percentage of

potential sites that lacked sialic acid as a terminal sugar, ranged from, 15% to 85%. After using the claimed invention, sialic acid occupied *greater than* 90% of possible sites.

Most of the work referred to by Dr. Zopf was carried out under agreements that prevent the public disclosure of the results of the methods. The results of the resialylation of a particular company under one such agreement were published, however.

Attached as Exhibit 3 to Dr. Zopf's Declaration is a copy of a presentation at the Biotechnology Industry Organization Meeting (BIO) held on June 26, 2001, in San Diego, California. As described therein, a "glycoprotein X" (GPX) was sent to Neose for resialylation. The purified GPX and the GPX prepared using the present process were physically characterized by eletrospray mass spectrometry. The two proteins' pharmacokinetic profiles were thereafter compared using bolus injections and continuous infusion into Cynomogus monkeys.

As explained in paragraphs 9-10, the resialyaltion of GPX was successful in restoring sialic acid on 99% of exposed Gal residues and N-linked glycans. By increasing N-linked sialylation of GPX, there was a concomitant slower plasma clearance; and an increase in steady-state plasma concentration.

In Dr. Zopf's opinion, this commercial success of the present invention is directly related to the innovative process and thus, a nexus between the claimed invention and evidence of commercial success has been established.

With the present response, Applicants also provide evidence of the continued commercial success of the present invention. Appendices 1-6 show that the assignee of the application continues to collaborate with partners based on the ability of the methods of the claimed invention to enhance activity of various therapeutic proteins.

Appendix 1 is a manuscript resulting from research carried out by Neose scientists in collaboration with scientists from Avant Immunotherapeutics. As a result of the glycosylation reactions described there (both sialylation and fucosylation), nearly all of the carbohydrates of the resulting protein terminated in the desired oligosaccharide structure (termed sLe^x). The proteins therefore had a ten-fold increase in affinity for the target receptor (termed E-selectin). The authors conclude that the *in vitro* glycosylation of the invention "reduces heterogeneity of

the glycan profile, improves pharmacokinetics and engances carbohydrate mediated binding to E-selection." (*see* Abstract).

Appendices 2-6 are press releases describing a collaborations between Neose and other companies. Appendix 2 describes a collaboration with MacroGenics to improve therapeutic properties of monoclonal antibodies. Appendix 3 describes a collaboration to improve a therapeutic protein made by NovoNordisk. Appendix 4 relates to a collaboration with Wyeth-Ayerst Laboratories to improve rPSGL. Appendix 5 is an announcement that the collaboration was terminated because of poor clinical trial results, unrelated to the Neose's Glycoadvance technology. Finally, Appendix 6 describes a collaboration with Monsanto to improve glycosylation on antibodies produced in plants.

Applicants have set forth evidence of the continued commercial success of the claimed invention. Moreover, the commercial success is directly derived from the invention claimed, in a marketplace where the consumer is free to choose on the basis of objective principles, and such success is not the result of heavy promotion or advertising, shift in advertising, consumption by purchasers normally tied to applicant or assignee, or other business events extraneous to the merits of the claimed invention. Thus, the Zopf Declaration and Appendices 1-6 establish a nexus between the claimed invention and evidence of commercial success.

Moreover, in view of the foregoing, it is evident that the present invention satisfies a long-felt need for providing methods for *in vitro* sialylation of saccharide groups present on recombinantly produced glycoproteins. Prior to the advent of the present invention, a long-felt need existed for an *in vitro* procedure to enzymatically cap carbohydrate chains that lacked a terminal sialic acid. The present invention satisfies this need.

As such, the foregoing secondary indicia represents objective evidence sufficient to rebut a *prima facie* case of obviousness. Accordingly, the Examiner is respectfully requested to withdraw the 35 U.S.C. §103(a) rejection and send this application to issue.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,

Kevin Bastian
Reg. No. 34,774

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
KLB:klb
60151663 v1